

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Shuji Jinno et al. Art Unit : 1626
Serial No. : 10/727,644 Examiner : Ebenezer Sackey
Filed : December 5, 2003
Title : TRICYCLIC FUSED HETEROCYCLE COMPOUNDS, PROCESS FOR
PREPARING THE SAME AND USE THEREOF

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT DATED MARCH 6, 2006

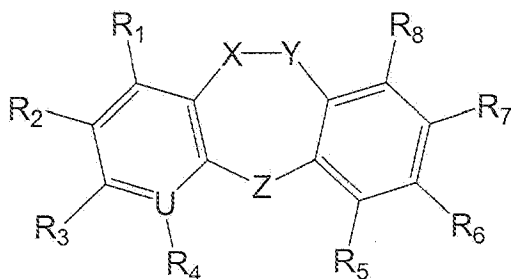
A Listing of Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 17 of this paper.

The following listing of claims corresponds to the claims currently on file.

Listing of claims

1. (Previously Presented) A compound represented by formula (1),



Formula 1

wherein

when the X-Y bond is a single bond, X and Y are independently selected from the group consisting of:

CW₁W₂ wherein W₁ and W₂ are independently selected from the group consisting of one of a hydrogen atom, a halogen, a hydroxyl group, a lower alkyl group, a substituted lower alkyl group, a lower alkoxy group, a cycloalkyl group and a cycloalkenyl group,

C=O, and

C=NOW₃ wherein W₃ is a hydrogen atom or a lower alkyl group;

when the X-Y bond is a double bond, X and Y are each independently CW₄ wherein W₄ is any one of a hydrogen atom, a halogen, a hydroxyl group, a lower alkyl group, a substituted lower alkyl group, a lower alkoxy group or an acyloxy group;

Z is O;

U is C;

R₁ to R₄ are independently selected from the group consisting of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group, a substituted cycloalkyl

group, a lower alkenyl group, a substituted lower alkenyl group, a lower alkynyl group, a substituted lower alkynyl group, a halogen, a lower alkylcarbonyl group, a substituted lower alkylcarbonyl group, a trihalomethyl group, V_1W_5 , a nitro group, an amino group, a substituted amino group, a cyano group, an acyl group, an acylamino group, a substituted acyl group, a substituted acylamino group, an aromatic ring, a substituted aromatic ring, a heterocycle and a substituted heterocycle wherein

V_1 is any one of O, S, S=O or SO_2 ,

W_5 is any one of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkylcarbonyl group and a substituted lower alkylcarbonyl group, an acyloxy group or a trihalomethyl group, and

R_5 to R_8 are independently selected from the group consisting of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkenyl group, a substituted lower alkenyl group, a lower alkynyl group, a substituted lower alkynyl group, a halogen, a lower alkylcarbonyl group, a substituted lower alkylcarbonyl group, a trihalomethyl group, V_2W_7 , a nitro group, an amino group, a substituted amino group, an acylamino group, an aromatic ring, a substituted aromatic ring, a heterocycle and a substituted heterocycle; wherein

V_2 is one of O, S, S=O or SO_2 ,

W_7 is one of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkylcarbonyl group, a substituted lower alkylcarbonyl group or a trihalomethyl group,

wherein:

when X is CHW_0 , CW_0W_0 or CW_0 at least one of R_5 to R_8 is a hydroxyl group, provided that at least one of R_5 , R_7 or R_8 is a hydroxy group when the X-Y bond is $CH(C_2H_5)CO$ and R_6 is a hydroxyl group and

when X is other than CHW_0 , CW_0W_0 or CW_0 at least one of R_5 to R_8 is a hydroxyl group and, at the same time, at least one of the other R_5 to R_8 is a group of OR wherein

W_0 is any one selected from the group consisting of a lower alkyl group and a substituted lower alkyl group and

R is any one selected from the group consisting of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkylcarbonyl group and a substituted lower alkylsilyl group; and

when X-Y is CH_2CH_2 , $CHBrCH_2$, CH_2CO , $CHBrCO$, $CH=CH$, $CH=COCOCH_3$ or $CH=COCH_3$,

at least one of R_1 to R_4 is an aromatic ring, a substituted aromatic ring, a heterocycle or a substituted heterocycle provided that when both R_6 and R_7 are hydroxyl groups, any one of R_1 to R_4 is not a phenyl group; or

at least one of R_1 to R_4 is SW_8 or $S(O)W_9$ wherein W_8 and W_9 independently are a lower alkyl group or a substituted lower alkyl group provided that R_7 is not a hydrogen atom when Z is O; or

R_2 is either a lower alkyl group or a substituted lower alkyl group and, at the same time, R_8 is a hydroxyl group provided that the number of carbon atoms of the lower alkyl group is 3 or more when Z is O; or

at least one of R_1 to R_4 is a lower alkylcarbonyl group provided that the number of carbon atoms of the lower alkyl group is 3 or more, a cycloalkylcarbonyl group or a cycloalkenylcarbonyl group and, at the same time, R_8 is a hydroxyl group; or

at least one of R_1 to R_4 is a cyano group; or

at least one of R_1 to R_4 is $-C(=NOR)CH_3$ wherein R is a hydrogen atom or a lower alkyl group, an optical isomer thereof, a conjugate thereof or a pharmaceutically acceptable salt thereof.

2. (Original) The compound according to claim 1, wherein R_6 is a hydroxyl group.

3. (Original) The compound according to claim 1, wherein R₆ and R₇ are hydroxyl groups.

4. (Original) The compound according to claim 1, wherein R₆ and R₈ are hydroxyl groups.

5. (Original) The compound according to claim 1, wherein R₅ and R₆ are hydroxyl groups.

6. (Previously Presented) The compound according to claim 1, wherein the X-Y bond is a single bond and X is CW₁W₂ or the X-Y bond is a double bond and X is CW, wherein

at least one of W₁ and W₂ is selected from the group consisting of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group and a cycloalkenyl group and

W is one of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group or a cycloalkenyl group.

7. (Previously Presented) The compound according to claim 1, wherein Y is CO.

8. (Previously Presented) The compound according to claim 6, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

9. (Previously Presented) The compound according to claim 1, wherein R₂ or R₃ is any one of a heterocycle, a substituted heterocycle, an aromatic ring or a substituted aromatic ring.

10. (Previously Presented) The compound according to claim 1, wherein the heterocycle is an aromatic heterocycle.

11. (Previously Presented) The compound according to claim 1, wherein R_2 or R_3 is SW_8 or $S(O)W_9$, wherein

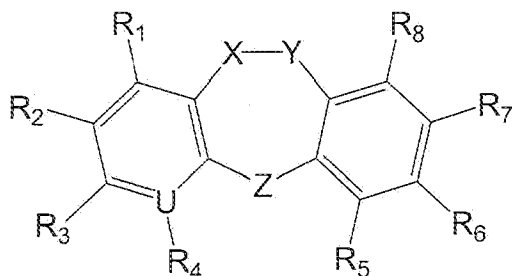
W_8 is a lower alkyl group or a substituted lower alkyl group, and

W_9 is a lower alkyl group or a substituted alkyl group.

12. (Previously Presented) The compound according to claim 11, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

13-16. (Cancelled)

17. (Previously Presented) A method of preparing a compound represented by formula (1),



Formula 1

wherein

when the X-Y bond is a single bond, X and Y are independently selected from the group consisting of:

CW_1W_2 wherein W_1 and W_2 are independently selected from the group consisting of one of a hydrogen atom, a halogen, a hydroxyl group, a lower alkyl group, a substituted lower alkyl group, a lower alkoxy group, a cycloalkyl group and a cycloalkenyl group,

$C=O$, and

$C=NOW_3$ wherein W_3 is a hydrogen atom or a lower alkyl group;

when the X-Y bond is a double bond, X and Y are each independently CW_4 wherein W_4 is any one of a hydrogen atom, a halogen, a hydroxyl group, a lower alkyl group, a substituted lower alkyl group, a lower alkoxy group or an acyloxy group;

Z is O;

U is C;

R_1 to R_4 , are independently selected from the group consisting of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group, a substituted cycloalkyl group, a lower alkenyl group, a substituted lower alkenyl group, a lower alkynyl group, a substituted lower alkynyl group, a halogen, a lower alkylcarbonyl group, a substituted lower alkylcarbonyl group, a trihalomethyl group, V_1W_5 , a nitro group, an amino group, a substituted amino group, a cyano group, an acyl group, an acylamino group, a substituted acyl group, a substituted acylamino group, an aromatic ring, a substituted aromatic ring, a heterocycle and a substituted heterocycle wherein

V_1 is any one of O, S, S=O or SO_2 ,

W_5 is any one of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkylcarbonyl group and a substituted lower alkylcarbonyl group, an acyloxy group or a trihalomethyl group, and

R_5 to R_8 are independently selected from the group consisting of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkenyl group, a substituted lower

alkenyl group, a lower alkynyl group, a substituted lower alkynyl group, a halogen, a lower alkylcarbonyl group, a substituted lower alkylcarbonyl group, a trihalomethyl group, V_2W_7 , a nitro group, an amino group, a substituted amino group, an acylamino group, an aromatic ring, a substituted aromatic ring, a heterocycle and a substituted heterocycle; wherein

V_2 is one of O, S, S=O or SO_2 ,

W_7 is one of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkylcarbonyl group, a substituted lower alkylcarbonyl group or a trihalomethyl group,

wherein:

when X is CHW_0 , CW_0W_0 or CW_0 at least one of R_5 to R_8 is a hydroxyl group, provided that at least one of R_5 , R_7 or R_8 is a hydroxy group when the X-Y bond is $CH(C_2H_5)CO$ and R_6 is a hydroxyl group and

when X is other than CHW_0 , CW_0W_0 or CW_0 at least one of R_5 to R_8 is a hydroxyl group and, at the same time, at least one of the other R_5 to R_8 is a group of OR wherein

W_0 is any one selected from the group consisting of a lower alkyl group and a substituted lower alkyl group and

R is any one selected from the group consisting of a hydrogen atom, a lower alkyl group, a substituted lower alkyl group, a lower alkylcarbonyl group and a substituted lower alkylsilyl group; and

when X-Y is CH_2CH_2 , $CHBrCH_2$, CH_2CO , $CHBrCO$, $CH=CH$, $CH=COCOCH_3$ or $CH=COCH_3$,

at least one of R_1 to R_4 is an aromatic ring, a substituted aromatic ring, a heterocycle or a substituted heterocycle provided that when both R_6 and R_7 are hydroxyl groups, any one of R_1 to R_4 is not a phenyl group; or

at least one of R_1 to R_4 is SW_8 or $S(O)W_9$ wherein W_8 and W_9 independently are a lower alkyl group or a substituted lower alkyl group provided that R_7 is not a hydrogen atom when Z is O; or

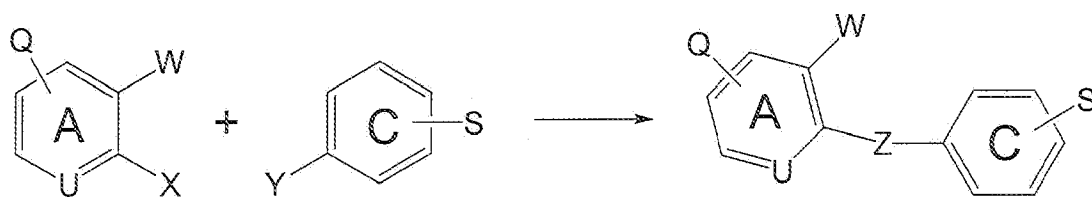
R_2 is either a lower alkyl group or a substituted lower alkyl group and, at the same time, R_8 is a hydroxyl group provided that the number of carbon atoms of the lower alkyl group is 3 or more when Z is O; or

at least one of R_1 to R_4 is a lower alkylcarbonyl group provided that the number of carbon atoms of the lower alkyl group is 3 or more, a cycloalkylcarbonyl group or a cycloalkenylcarbonyl group and, at the same time, R_8 is a hydroxyl group; or

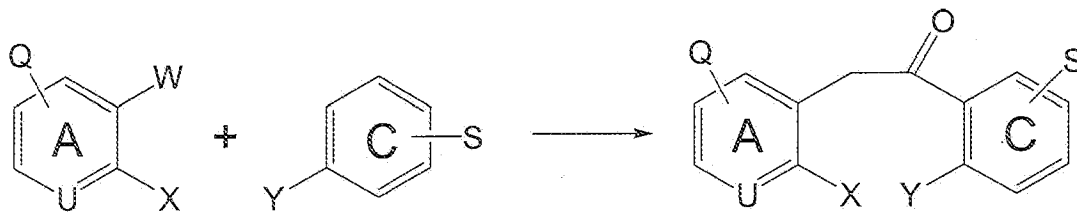
at least one of R_1 to R_4 is a cyano group; or

at least one of R_1 to R_4 is $-C(=NOR)CH_3$ wherein R is a hydrogen atom or a lower alkyl group, an optical isomer thereof, a conjugate thereof or a pharmaceutically acceptable salt thereof,

which comprises, in any order, the reaction steps of (1) bonding a ring A to a ring C by the Ullmann reaction as shown in formula 2 and (2) bonding a ring A to a ring C by the Friedel-Crafts reaction or photoreaction as shown in formula 3,



Formula 2



Formula 3

wherein

Q, S and W are each any substituent;

U is C;

one of X and Y is a leaving group and the other is a nucleophilic group; and

Z is O.

18. (Previously Presented) The method according to claim 17 further comprising at least one of a carbon atom increasing reaction, a conversion reaction of a substituent, an introduction reaction of a substituent, a removal of the protection of a substituent, forming a salt, and performing optical resolution.

19. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

20. (Previously Presented) The pharmaceutical composition according to claim 19 wherein the pharmaceutical composition utilizes the tracheal smooth muscles relaxing action of the compound.

21. (Previously Presented) The pharmaceutical composition according to claim 19 wherein the pharmaceutical composition utilizes the inhibitory effect on airway hypersensitivity of the compound.

22. (Previously Presented) The pharmaceutical composition according to claim 19 wherein the pharmaceutical composition utilizes the inhibitory effect on inflammatory cells infiltration of the compound.

23. (Previously Presented) The pharmaceutical composition according to claim 19 wherein the pharmaceutical composition is used as the anti-asthmatic drug.

24 -25. (Cancelled)

26. (Previously Presented) The compound of claim 1 wherein X and Y are the same.

27. (Previously Presented) The compound of claim 1 wherein X and Y are different.

28. (Previously Presented) The compound of claim 1 wherein W_1 and W_2 are the same.

29. (Previously Presented) The compound of claim 1 wherein W_1 and W_2 are different.

30. (Previously Presented) The compound of claim 1 wherein R_1 to R_4 are the same.

31. (Previously Presented) The compound of claim 1 wherein R_1 to R_4 are different.

32. (Previously Presented) The compound of claim 1 wherein R_5 to R_8 are the same.

33. (Previously Presented) The compound of claim 1 wherein R_5 to R_8 are different.

34. (Previously Presented) The compound according to claim 2, wherein the X-Y bond is a single bond and X is CW_1W_2 or the X-Y bond is a double bond and X is CW , wherein

at least one of W_1 and W_2 is selected from the group consisting of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group and a cycloalkenyl group and

W is one of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group or a cycloalkenyl group.

35. (Previously Presented) The compound according to claim 3, wherein the X-Y bond is a single bond and X is CW_1W_2 or the X-Y bond is a double bond and X is CW, wherein

at least one of W_1 and W_2 is selected from the group consisting of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group and a cycloalkenyl group and

W is one of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group or a cycloalkenyl group.

36. (Previously Presented) The compound according to claim 4, wherein the X-Y bond is a single bond and X is CW_1W_2 or the X-Y bond is a double bond and X is CW, wherein

at least one of W_1 and W_2 is selected from the group consisting of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group and a cycloalkenyl group and

W is one of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group or a cycloalkenyl group.

37. (Previously Presented) The compound according to claim 5, wherein the X-Y bond is a single bond and X is CW_1W_2 or the X-Y bond is a double bond and X is CW, wherein

at least one of W_1 and W_2 is selected from the group consisting of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group and a cycloalkenyl group and

W is one of a lower alkyl group, a substituted lower alkyl group, a cycloalkyl group or a cycloalkenyl group.

38. (Previously Presented) The compound according to claim 2, wherein Y is CO.

39. (Previously Presented) The compound according to claim 3, wherein Y is CO.

40. (Previously Presented) The compound according to claim 4, wherein Y is CO.

41. (Previously Presented) The compound according to claim 5, wherein Y is CO.

42. (Previously Presented) The compound according to claim 6, wherein Y is CO.

43. (Previously Presented) The compound according to claim 1, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

44. (Previously Presented) The compound according to claim 2, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

45. (Previously Presented) The compound according to claim 3, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

46. (Previously Presented) The compound according to claim 4, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

47. (Previously Presented) The compound according to claim 5, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

48. (Previously Presented) The compound according to claim 6, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group or a *tert*-butyl group.

49. (Previously Presented) The compound according to claim 2, wherein R₂ or R₃ is any one of a heterocycle, a substituted heterocycle, an aromatic ring or a substituted aromatic ring.

50. (Previously Presented) The compound according to claim 3, wherein R₂ or R₃ is any one of a heterocycle, a substituted heterocycle, an aromatic ring or a substituted aromatic ring.

51. (Previously Presented) The compound according to claim 4, wherein R_2 or R_3 is any one of a heterocycle, a substituted heterocycle, an aromatic ring or a substituted aromatic ring.

52. (Previously Presented) The compound according to claim 5, wherein R_2 or R_3 is any one of a heterocycle, a substituted heterocycle, an aromatic ring or a substituted aromatic ring.

53. (Previously Presented) The compound according to claim 2, wherein R_2 or R_3 is SW_8 or $S(O)W_9$, wherein

W_8 is a lower alkyl group or a substituted lower alkyl group, and

W_9 is a lower alkyl group or a substituted alkyl group.

54. (Previously Presented) The compound according to claim 3, wherein R_2 or R_3 is SW_8 or $S(O)W_9$, wherein

W_8 is a lower alkyl group or a substituted lower alkyl group, and

W_9 is a lower alkyl group or a substituted alkyl group.

55. (Previously Presented) The compound according to claim 4, wherein R_2 or R_3 is SW_8 or $S(O)W_9$, wherein

W_8 is a lower alkyl group or a substituted lower alkyl group, and

W_9 is a lower alkyl group or a substituted alkyl group.

56. (Previously Presented) The compound according to claim 5, wherein R_2 or R_3 is SW_8 or $S(O)W_9$, wherein

W_8 is a lower alkyl group or a substituted lower alkyl group, and

W_9 is a lower alkyl group or a substituted alkyl group.

57. (Previously Presented) The compound according to claim 56, wherein the lower alkyl group is any one of a methyl group, an ethyl group, a *n*-propyl group, an isopropyl group, an *n*-butyl group, a *sec*-butyl group, an isobutyl group, or a *tert*-butyl group.

58. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 2 and a pharmaceutically acceptable carrier or diluent.

59. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 3 and a pharmaceutically acceptable carrier or diluent.

60. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 4 and a pharmaceutically acceptable carrier or diluent.

61. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 5 and a pharmaceutically acceptable carrier or diluent.

62. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 6 and a pharmaceutically acceptable carrier or diluent.

63. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 7 and a pharmaceutically acceptable carrier or diluent.

64. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 8 and a pharmaceutically acceptable carrier or diluent.

65. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 9 and a pharmaceutically acceptable carrier or diluent.

66. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 10 and a pharmaceutically acceptable carrier or diluent.

67. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 11 and a pharmaceutically acceptable carrier or diluent.

68. (Previously Presented) A pharmaceutical composition comprising an effective amount of the compound of claim 12 and a pharmaceutically acceptable carrier or diluent.

REMARKS

Claims 1-12, 17-23 and 26-68 are pending, with claims 1 and 17 being independent.
Claims 13-16 and 24-25 were previously cancelled.

Applicant notes that the restriction requirement does not account for the preliminary amendment that was filed with the application, and that the claims of Group III were previously canceled.

Applicant hereby elects the invention of Group I, which includes claims 1-12, 19-23 and 26-68.

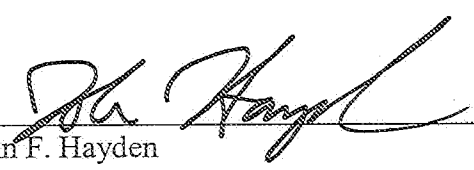
In addition, applicant elects the set of compounds represented by formula 1, where X is CW_1W_2 , W_1 and W_2 are each a hydrogen atom, Y is C=O, Z is O, U is C, any one of R_1 to R_4 is a herocycle and the others are a hydrogen atom, and any two of R_5 to R_8 are V_2W_7 where V_2 is O and W_7 is a hydrogen atom (i.e., V_2W_7 is OH), and the others are each a hydrogen atom. Examples of this set of compounds include those of examples 5, 55, 57, 58, 70, 110, 114 and 115.

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Respectfully submitted,

Date: _____

4/6/06



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